Remarks

Prior to this amendment, claims 1, 6-9, 11, 13-15, 21, 26-28, 32-34, and 38-45 were pending in this application. Claim 26 is amended herein. Support for the amendment of claim 26 can be found in the specification at page 19, lines 24-29.

No new matter has been added by these amendments. After entry of this amendment, **claims 1, 6-9, 11, 13-15, 21, 26-28, 32-34, and 38-45 are pending**. Unless specifically stated otherwise, none of these amendments are intended to limit the scope of any claim; Applicants reserve the right to pursue any removed subject matter in a related application.

Claim Rejections Under 35 U.S.C. §112, second paragraph

Claims 26-28 are rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants traverse this rejection.

Claim 26 is rejected for allegedly not being clear because the claimed enhanced immune cell activity is not correlated with increased tumor immunosurveillance. Solely to advance prosecution in this case, claim 26 is amended to recite that blocking the TGF-β signaling pathway results in "increased activity of the immune cell, wherein the increased activity is increased tumor immunosurveillance." Thus, the enhanced activity of the immune cell is correlated with increased tumor immunosurveillance. In light of the amendment, Applicants submit that claim 26 is clear and definite and withdrawal of the rejection is respectfully requested. Claims 27 and 28 depend from claim 26 and incorporate all the limitations thereof.

Claim Rejections Under 35 U.S.C. §112, first paragraph (enablement)

The previous rejection of claims 39-45 under 35 U.S.C. §112, as allegedly failing to comply with the enablement requirement, has been maintained. Applicants traverse this rejection.

Claims 39-45 are directed to a method of screening for an agent that inhibits tumor recurrence. The Office action alleges that "Applicant's specification has not provided any examples of such a screening process nor has the monoclonal antibody used in the treatment aspect of the specification been used in the screening assay . . . Applicant has not even provided any *in vitro* data. Even if applicant had provided *in vitro* data, one could not extrapolate this teaching to *in vivo* use because the *in vitro* experimental data would not be drawn to subjects with tumor cells . . . Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions" (Office action dated June 8, 2007, at page 4 and page 5).

Based on the above statement, Applicants believe that the Office is requiring that the claimed invention be reduced to practice in order to demonstrate that the invention is enabled. However, MPEP §2164.02 clearly states that "[a]n applicant need not have actually reduced the invention to practice prior to filing. In *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987)" and that "lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement." Thus, the lack of data or examples of a screening process is not sufficient to reject the claims for lack of enablement.

MPEP §2164.02 also states that "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)." Applicants submit that the specification provides all the information necessary for one of skill in the art to perform the claimed screening method without undue experimentation. For example, the specification provides:

(i) various *in vitro* and *in vivo* screening methods for identifying which agents can inhibit tumor recurrence (page 26, line 5 through page 27, line 18);

(ii) representative candidate agents that can be used to block the TGF-beta signaling pathway and inhibit tumor recurrence (page 22, line 31 through page 24, line 20);

(iii) example *in vitro* assays to measure the effect of such agents on the TGF-beta signaling pathway (page 24, line 23 through page 25, line 5); and

(iv) example *in vivo* assays to measure the effect of such agents on the TGF-beta signaling pathway (page 25, lines 7-38).

Thus, Applicants contend that the specification provides sufficient guidance for one of skill in the art to understand and perform the claimed screening methods in order to identify an agent that can inhibit tumor recurrence.

Further, at the time the application was filed it was well known to those of skill in the art how to use *in vitro* assays to test the effectiveness of various agents for clinical use. It was also well known at the time how to test promising candidate agents *in vivo* using any one of a number of animal models. Thus, Applicants submit that, given the state of the art at the time of filing and the guidance in the specification, it would merely be **routine** to perform the method of screening for an agent that inhibits tumor recurrence, particularly in view of Applicants' specific teachings in the specification.

In light of the above arguments, Applicants submit that claims 39-45 are fully enabled by the specification. Applicants request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Claim Rejections Under 35 U.S.C. §103

Dasch *et al.* in view of Barbera-Guillem, Rosenblum, and Zavada *et al.*

Claims 1, 6-9, 11, 13-15, 21, 26-28, and 32-34 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Dasch *et al.* (U.S. Patent No. 6,090,383) in view of Barbera-Guillem (U.S. Patent No. 6,224,866), Rosenblum (U.S. Patent Application No. 2005/0214307), and Zavada *et al.* (U.S. Patent No. 6,297,041) because the combination of references teach "that compounds that treat tumors can also be used to treat tumor recurrence" (Office action at page 5). Applicants strenuously traverse this rejection.

The United States Patent and Trademark Office has provided Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co.* v. *Teleflex Inc.* Based on those Guidelines, the Office must provide the appropriate rationale to support rejections under 35 U.S.C. 103.

As discussed in the Office action, Dasch *et al.* does not specifically discuss the treatment of tumor recurrence.[1] However, the Office action alleges that it is "known in the art that compounds that treat tumors can also be used to treat tumor recurrence" (Office action at page 5) and combines Dasch *et al.* with three other references (Barbera-Guillem, Rosenblum, and Zavada *et al.*) which allegedly make up for the deficiency of Dasch *et al.* Applicants respectfully disagree.

Applicants submit that not all of the claimed elements were known in the prior art and therefore the claimed elements would not have been combined, in view of Dasch *et al.*, Barbera-Guillem, Rosenblum, and Zavada *et al.*, to predictably yield the claimed invention. For example, the Office alleges that "Barbera-Guillem discloses that one skilled in the art would readily recognize that the same procedure used for treating a cancer would also be used for the treatment of recurrence of the same cancer (col. 23, lines 20-25)." Applicants note that the claims are directed to methods of *inhibiting* a tumor recurrence and <u>not</u> to the *treatment* of a tumor recurrence. Applicants submit that treating a recurrence is not equivalent to inhibiting or preventing a recurrence. In support of this argument, Applicants submit herewith a Declaration under 37 C.F.R. 1.132, from Inventor Jay A. Berzofsky, M.D., Ph.D. (Declaration). As discussed in the Declaration, one of skill in the art would not expect that an agent effective at *treating* a tumor recurrence would also be effective at *inhibiting* a tumor recurrence (see Declaration at paragraph 8). Because Barbera-Guillem only discloses that the same agent can be used to *treat* both the primary tumor and the recurrence, and does not teach that the same agent can *inhibit* the recurrence, this reference does not overcome the deficiencies of Dasch *et al.* Moreover, because it is well known in the art that different agents may be required to inhibit a tumor recurrence and treat a tumor recurrence, it would not have been obvious to one of skill in

[1] Nor does Dasch *et al.* disclose methods of *inhibiting* tumor recurrence.

the art to try to use a treatment agent in order to inhibit tumor recurrence (see Declaration at paragraphs 8 and 9).

Zavada *et al.* discloses the use of antibodies directed against an oncoprotein (the MN protein) to treat cancer patients expressing the MN protein (column 10, lines 42-44). Zavada *et al.* also discloses the use of a different class of antibody, anti-idiotype antibodies to MN-specific antibodies, in a vaccine to inhibit recurrence of a MN-expressing tumor (column 10, lines 5-9). An anti-MN protein antibody is not the same agent (and does not target the same antigen) as an anti-idiotype antibody which recognizes an MN-specific antibody. Thus, because Zavada *et al.* does not disclose that one specific agent can be used to both treat a tumor and inhibit a recurrence, one of skill in the art would not have predicted the claimed method in view of this reference.

Rosenblum discloses that one specific agent (an immunoconjugate comprised of a single chain antibody linked to a cytotoxic moiety, where the antibody targets the cytotoxic moiety to the tumor cell) used in the treatment of tumors can be used to prevent tumor recurrence (paragraph [0043]). However, the mere fact that Rosenblum (or Zavada *et al.*) discloses an antibody that targets a tumor protein is not, on its own, predictive of the claimed method, which uses a completely different antibody. Moreover, in contrast to Rosenblum and Zavada *et al.*, the antibody of the claimed method blocks an immunosuppressive effect of TGF-beta and does not directly target a tumor cell or a tumor protein. For example, the specification of the subject application clearly discloses that up-regulation of TGF-beta production in tumor-bearing mice occurs in non-lymphoid $CD11b^{+}Gr\text{-}1^{+}$ cells, that $Gr\text{-}1^{+}$ cells were involved in the down-regulation of immunosurveillance *in vivo*, and that depletion of $CD11b^{+}Gr\text{-}1^{+}$ cells almost completely abrogated TGF-beta production from these non-lymphoid cells (specification at page 36, lines 22-30; page 37, lines 5-6). A study of the morphology of $CD11b^{+}Gr\text{-}1^{+}$ cells identified the TGF-beta over-expressing $CD11b^{+}Gr\text{-}1^{high}$ cells as primarily mature and some immature neutrophils, and $CD11b^{+}Gr\text{-}1^{int}$ cells as primarily immature myeloid cells and some immature monocytes (specification at page 38, lines 4-8). Thus, the antibody used in the claimed method does not target a tumor protein and acts via a completely different mechanism than the antibodies

disclosed in Rosenblum and Zavada *et al.* Neither Rosenblum nor Zavada *et al.* disclose an antibody that blocks an immunosuppressive effect of TGF-beta, as required by the claims.

Applicants submit that, in view of the disclosures of Rosenblum or Zavada *et al.*, it would not have been obvious to one of skill in the art to have substituted the antibodies disclosed in these references with an antibody that blocks an immunosuppressive effect of TGF-beta in order to inhibit a recurrence of a tumor. Similarly, in view of the disclosures of Rosenblum or Zavada *et al.*, it would not have been obvious to one of skill in the art to try to use an antibody that does not bind a tumor protein in order to inhibit recurrence of a tumor.

As discussed above, Dasch *et al.* does not disclose treating or inhibiting tumor recurrence. Applicants respectfully submit that the disclosures of Rosenblum and Zavada *et al.* are not relevant to the claimed invention and should not be combined with Dasch *et al.* Barbera-Guillem does not overcome the deficiencies of Dasch *et al.* Accordingly, Applicants requests that the rejection be withdrawn.

Dasch *et al.* in view of Barbera-Guillem, Rosenblum, Zavada *et al.*, and Suthanthiran *et al.*

Claims 1, 6-11, 13-15, 21, 26-28, 32-34 and 38 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Dasch *et al.* in view of Barbera-Guillem, Rosenblum, Zavada *et al.* and Suthanthiran *et al.* (U.S. Publication No. US 2004-0197333). Applicants respectfully traverse this rejection.

The Office action states that Suthanthiran *et al.* discloses the use of TGF-beta antagonists, including monoclonal antibodies, "to *treat* a variety of different cancers known to be associated with TGF-beta" (Office action at page 7, emphasis added). However, Suthanthiran *et al.* does not teach the use of TGF-beta antagonists to *inhibit the recurrence* of a tumor that has escaped tumor immunosurveillance. Nor does Suthanthiran *et al.* disclose the concept of tumor recurrence.

As discussed above, Dasch *et al.* alone does not teach all of the limitations of the claims. The disclosures of Barbera-Guillem, Rosenblum, and Zavada *et al.* are not relevant to the use of

an antibody to block an immunosuppressive effect of TGF-beta in order to inhibit recurrence of a tumor and should not be combined with Dasch *et al.* Because neither Dasch *et al.* nor Suthanthiran *et al.* implicitly or explicitly teach all elements of the claimed methods, Applicants' claims are non-obvious over the cited references. Withdrawal of this rejection is requested.

Dasch *et al.* in view of Barbera-Guillem, Rosenblum, Zavada *et al.*, and Terabe *et al.*

Claims 1, 6-9, 11, 13-18, 21, 26-28, 32-34 and 38 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Dasch *et al.* in view of Barbera-Guillem, Rosenblum, Zavada *et al.* and Terabe *et al.* (*Nature Immunology*, 1:515-520, 2000). Applicants respectfully traverse this rejection.

The Office action states that the Terabe *et al.* shows that the "assays of claims 16-18 are known in the art . . . and are used in tumor immunosurveillance" (Office action at page 8). However, Terabe *et al.* does not teach the use of TGF-beta antagonists to *inhibit the recurrence* of a tumor that has escaped tumor immunosurveillance. As discussed above, Dasch *et al.* does not teach methods of inhibiting tumor recurrence. In addition, the disclosures of Barbera-Guillem, Rosenblum, and Zavada *et al.* are not relevant to the claimed invention and should not be combined with Dasch *et al.* In light of the above discussion, Applicants' claims are non-obvious over the cited references. Withdrawal of this rejection is requested.

Request for Examiner Interview

Applicants believe the application is in condition for allowance and such action is requested. If an additional rejection is asserted, or if the present rejections are maintained, Examiner Huff is formally requested to contact the undersigned in order to arrange a telephonic interview prior to issuance of the next Office action. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview can be arranged in advance by a written request.

Respectfully submitted,

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